

CLAIMS

What is claimed is:

1. A cell population, comprising differentiated cells derived from induced pluripotent stem cells, said differentiated cells having a Natural Killer cell phenotype (iNK cells), wherein the iNK cells comprise an inactivating mutation in the *TGFbR2* gene, and wherein the iNK cells express interleukin-15 (IL-15) or a functional fragment thereof.
2. The cell population of claim 1, wherein the iNK cells comprise a homozygous inactivating mutation in the *TGFbR2* gene.
3. The cell population of claim 1, wherein the iNK cells comprise a heterozygous inactivating mutation in the *TGFbR2* gene.
4. The cell population of any one of claims 1-3, wherein the iNK cells express a cell membrane-bound form of IL-15 (mbIL-15) or functional fragment thereof.
5. The cell population of any one of claims 1-3, wherein the iNK cells express a cell membrane-bound form of IL-15 (mbIL-15) or functional fragment thereof fused to the IL-15 Receptor alpha (IL-15R α).
6. The cell population of any one of claims 1-3, wherein the iNK cells express IL-15 trapped in the endoplasmic reticulum (ER).
7. The cell population of any one of claims 1-3, wherein the iNK cells express a soluble form of IL-15 or functional fragment thereof.
8. The cell population of any one of claims 1-7, wherein the iNK cells comprise a knock-in of a polynucleotide encoding the IL-15 or functional fragment thereof into the *B2M* gene of the iPSC-NK cells.
9. The cell population of any one of claims 1-7, wherein the iNK cells comprise a knock-in of a polynucleotide encoding the IL-15 or functional fragment thereof into the *TGFbR2* gene of the iPSC-NK cells.
10. The cell population of claim 8 or 9, wherein the polynucleotide encoding the IL-15 or functional fragment thereof is operably linked to a promoter.

11. The cell population of claim 10, wherein the promoter is an exogenous promoter.
12. The cell population of claim 10, wherein the promoter is a constitutive promoter.
13. The cell population of claim 10, wherein the promoter is an EF1 α promoter (short version) or an EF1 α promoter (long version).
14. The cell population of claim 10, wherein the promoter is an endogenous promoter.
15. The cell population of any one of claims 1-14, wherein the expression level of TGFbR2 in the iNK cells is about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95% lower than the expression level of TGFbR2 in a population of unedited NK cells.
16. The cell population of any one of claims 1-15, wherein at least 50%, at least 55%, at least 60%, at least 65%, or at last 70%, of cells express one or more NK cell marker selected from the group consisting of CD56 and CD45.
17. A method of producing a cell population comprising differentiated cells derived from induced pluripotent stem cells, said differentiated cells having a Natural Killer cell phenotype (iNK cells), wherein the iNK cells comprise an inactivating mutation in the *TGFbR2* gene, and wherein the iNK cells express interleukin-15 (IL-15) or a functional fragment thereof, the method comprising (i) genetically editing a population of induced pluripotent stem cells (iPSCs); (ii) generating a monoclonal population of edited iPSCs; and (iii) differentiating said population of iPSCs into a population of Natural Killer (NK) cells.
18. The method of claim 17, wherein step (i) comprises introducing a polynucleotide encoding a soluble form of interleukin-15 (IL-15) or a functional fragment thereof.
19. The method of claim 17, wherein step (i) comprises introducing a polynucleotide encoding a cell membrane-bound form of IL-15 (mbIL-15) or functional fragment thereof.
20. The method of claim 17, wherein step (i) comprises introducing a polynucleotide encoding mbIL-15 or functional fragment thereof fused to IL-15R α .
21. The method of claim 17, wherein step (i) comprises introducing a polynucleotide encoding a form of IL-15 trapped in the endoplasmic reticulum (ER).

22. The method of any one of claims 17-21, wherein the IL-15 or functional fragment thereof is introduced using a TALEN construct.
23. The method of any one of claims 17-21, wherein the IL-15 is introduced using a Cas9 or Cas12 enzyme.
24. The method of any one of claims 17-21, wherein the IL-15 is introduced using a Dualase platform.
25. The method of any one of claims 17-24, wherein step (i) further comprises introducing a deletion in the *TGFbR2* gene of the genome of the iPSCs.
26. The method of any one of claims 17-25, wherein the method results in a cell population wherein the expression level of TGFBR2 in the iNK cells is about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95% lower than the expression level of TGFBR2 in a population of unedited NK cells.
27. The method of any one of claims 17-26, wherein at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or more than 98% of cells express one or more NK cell marker selected from the group consisting of CD56 and CD45.
28. A cell population produced by the method of any one of claims 17-27.
29. A pharmaceutical composition comprising the cell population of any one of claims 1-16 and 28.
30. Use of the pharmaceutical composition of claim 29 in the manufacture of a medicament for treating cancer in a subject in need thereof.
31. The use of claim 30, wherein the cancer is a solid tumor.
32. The use of claim 30, wherein the cancer is a hematological malignancy.
33. Use of the pharmaceutical composition of claim 29 in the manufacture of a medicament for inhibiting proliferation of tumor cells in a subject in need thereof.
34. The use of any one of claims 30-33, wherein the subject is to be further administered with an immune checkpoint inhibitor.

35. The use of claim 34, wherein the immune checkpoint inhibitor is an anti-PD-1 antibody, an anti-PDL-1 antibody, or an anti-CTLA-4 antibody.
36. The use of any one of claims 30-33, wherein the subject is to be further administered with an NK cell engager.
37. The use of claim 36, wherein the NK cell engager is an NKp46 NK cell engager.
38. The use of any one of claims 30-33, wherein the subject is to be further administered with an antibody.